

The stated purpose of the claims is to treat or inhibit atherosclerosis. The claims do not cover every conceivable means for achieving this stated purpose. The claims severely limit the way to effect the treatment of atherosclerosis. The claims specifically require an agent which can inhibit interaction between P-selectin and its ligand, and between E-selectin and its ligand. By inhibiting interaction is meant that the selectin and ligand are unable to properly bind to each other to effect proper formation of atherosclerotic lesions. See specification at page 7, lines 31-34. There are only a finite number of agents which have these properties. The specification describes the specific classes of agents which are covered by the claims. See, e.g., the specification at page 8, line 20 through page 12, line 20.

35 U.S.C. §112, second paragraph

Claims 13, 25 and 41 have been rejected under 35 U.S.C. §112, second paragraph.

The Examiner states that: "Claim 13 is unclear as to the intended meanings of "a portion of said P-selectin" and "a portion of said ligand of P-selectin." Applicants respectfully traverse this rejection. Claim 13 recites that the agent is "a soluble form of at least a portion of said P-selectin" or "a soluble form of at least a portion of the ligand of P-selectin." It is well known that words in a claim should be given their

ordinary and accustomed meaning unless it appears that the inventor used them differently. (See, e.g., *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753 (Fed. Cir. 1984). In the instant situation, the ordinary meaning of "a portion" of P-selectin or "a portion" of the ligand is "a part" or "a fragment" of the respective molecules. See, e.g., attached Exhibit I, Webster's Third New International Dictionary, where a definition of "portion" is "part of a whole." The meaning of a "part of a whole" (i.e., portion) of a molecule is clear to one skilled in the art.

The Examiner also states that "Claim 25 is unclear as to the identify of the intended agent, specifically insofar as how it is to be 'derived from' snake venom or a plant extract." Applicants respectfully traverse this rejection. It was well-known by those skilled in the art at the time that applicants' application was filed how to "derive" substances, i.e., isolate substances, from snake venoms and plant extracts. The specification states at page 11, lines 27-29 that: "Agents are also meant to include substances derived from natural products, such as snake venoms and plant extracts, that inhibit P-selectin with its ligand." And, it was well-known by those skilled in the art how to determine if a substance inhibits P-selectin with its ligand. See, e.g., Exhibit A (Cecconi et al., *J. Biol. Chem.* 269:15060-15066 (1994) and Exhibit B (Lenter et al., *J. Cell Biol.* 125:471-

481 (1994), which were filed with the Preliminary Amendment on October 10, 1997. See also the specification at page 12, line 27 through page 15, line 35.

The Examiner has not indicated why claim 41 was rejected under 35 U.S.C. §112, second paragraph, and therefore applicants cannot respond to this rejection.

35 U.S.C. §103(a)

Claims 1-13, 19, 20, 23-38 and 40-47 have been rejected under 35 U.S.C. §103 as being unpatentable over Kogan, Rao or Seekamp, in view of Ross, and further in view of Johnson-Tidey.

The Examiner states:

Each of Kogan, Rao and Seekamp teaches oligosaccharides or their derivatives which may be used to block interaction of selectins with their ligands.... None of Kogan, Rao or Seekamp teaches that blocking the interaction of P-selectin or E-selectin with their ligands is useful specifically for treatment or prevention of atherosclerosis.... Ross confirms that the prior art had recognized the role of adhesion molecules such as selectins in atherogenesis.... Johnson-Tidey discloses that P-selectin and E-selectin are expressed in atherosclerotic lesions.

Applicants respectfully traverse this rejection.

Claim 1 is directed to a method of treating or inhibiting atherosclerosis comprising providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin and between E-selectin and a ligand of E-selectin, and administering

the agent to a mammal in need of such treatment so as to cause such inhibition to occur.

Applicants' claimed invention has unique advantages over the prior art. The use of an agent which inhibits interaction of both P and E selectins gives the unexpected and surprising result of an additive effect in treating atherosclerosis. See, e.g., Exhibit K which was filed with the Preliminary Amendment on October 10, 1997. Exhibit K consists of five figures illustrating the results of experiments performed by the inventors on mice which were deficient in both P-selectin and E-selectin, as opposed to being deficient just for P-selectin, in inhibiting atherosclerotic lesions on the arterial walls. Fig. 1 illustrates that the size of aortic sinus lesions in LDL-receptor (LDLR)-deficient mice on an atherogenic (high cholesterol and fat) diet is significantly smaller in P- and E-selectin double deficient mice than in wild type or just P-selectin-deficient mice. Fig. 2 consists of photographs of entire aortae of LDLR-deficient mice on an atherogenic diet, and illustrates that the percentage area of the aortae that have atherosclerotic lesions is significantly smaller in P- and E-selectin double deficient mice than in wild type mice. Fig. 3 illustrates that there are significantly smaller aortic sinus lesions in LDLR-deficient mice on an atherogenic diet in P- and E-selectin double deficient mice than in wild type or just P-selectin-deficient mice. Fig. 4 illustrates that the size of

atherosclerotic lesions in the aortic sinus of LDLR-deficient mice, as a function of the length of time on an atherogenic diet, is significantly smaller for up to at least 37 weeks, in P- and E-selectin double deficient mice than in wild type or P-deficient mice. Fig. 5 illustrates that the percentage of mice with calcification in the aortic sinus of LDLR-deficient mice on an atherogenic diet, is significantly less in P- and E-selectin double deficient mice than in wild type mice. See also \$1.132 Declaration by Wagner, ¶14, filed with the Preliminary Amendment on October 10, 1997.

Kogan teaches certain compounds that inhibit the binding of E-selectin and/or P-selectin to sialyl Lewis. Kogan does not teach a method for treating atherosclerosis comprising administering an agent that inhibits both P and E selectins.

Rao teaches that certain derivatives of anthraquinone and anthracene can inhibit the binding of P, L and E selectins to sialyl-Lewis. Rao does not teach a method for treating atherosclerosis comprising administering an agent that inhibits both P and E selectins.

Seekamp teaches the role of P, L and E selectins in ischemia-reperfusion injury. Seekamp does not teach a method for treating atherosclerosis comprising administering an agent that inhibits both P and E selectins.

Ross is a general review article on atherosclerosis. Ross

does not teach a method for treating atherosclerosis comprising administering an agent that inhibits both P and E selectins.

Johnson-Tidey teaches that P-selectin expression is elevated in atherosclerotic endothelium. While Johnson-Tidey may show that there is a correlation between the presence of P-selectin and atherosclerotic plaques, there is no teaching that P-selectin causes the atherosclerosis, as opposed to the presence of P-selectin just being an effect of the atherosclerosis. Nor is there any teaching that inhibiting P-selectin interaction with its ligand will treat atherosclerosis. Moreover, with regards to E-selectin, while Johnson-Tidey states that E-selectin has also been found to be increased in human atherosclerotic lesions (page 952, col. 2, lines 13-15), Johnson-Tidey also states:

The competence of P-selectin and ICAM-1 to induce leukocyte traffic in chronic inflammation is further supported by the findings of Miyazaki et al. in autoimmune thyroid disease. Small vessels were found to be positive for both P-selectin and ICAM-1, but not E-selectin or vascular cell adhesion molecule-1, and the P-selectin expression correlated with the degree of mononuclear inflammatory cell infiltration into the thyroid glands. This selective expression of P-selectin and ICAM-1 in chronic inflammation has particular relevance for atherosclerosis, as variable and mostly low levels of E-selectin and vascular cell adhesion molecule-1 have been detected in the arterial endothelium over the plaques (page 959, col. 2, lines 4-17). (Emphasis added).

Thus, Johnson-Tidey is making an analogy between chronic inflammation in autoimmune thyroid disease and chronic

inflammation in atherosclerosis. Johnson-Tidey states that small vessels in autoimmune thyroid disease have been found to be positive for P-selectin and ICAM-1, but not for E-selectin or vascular cell adhesion molecule-1. And, similarly, Johnson-Tidey states that while there is selective expression for P-selectin and ICAM-1 in atherosclerosis, there is only variable and mostly low levels of E-selectin and vascular cell adhesion molecule-1 detected in the arterial endothelium over the plaques. Thus, Johnson-Tidey is distinguishing P-selectin and ICAM-1 from E-selectin and vascular cell adhesion molecule-1. Johnson-Tidey is actually teaching away from treating atherosclerosis with an agent that inhibits both P-selectin and E-selectin.

In sum, none of the cited prior art, either singly or in combination, teaches or suggests a method for treating or inhibiting atherosclerosis by providing an agent which inhibits interaction between P-selectin and its ligand and between E-selectin and its ligand. Even if one made the combination suggested by the Examiner, it would not meet the limitations recited in the claims under rejection. Most significantly, there is no teaching or suggestion whatsoever in the cited prior art of the advantages that are present in applicants' claimed invention, i.e., that an inhibitor of P-selectin and E-selectin has additive effects in treating atherosclerosis (as shown in Exhibit K, Figs. 1-5, discussed above). Such additive effects resulting from

applicants' claimed invention are unexpected and surprising.

Since claims 2-13, 19, 20, 23-37 and 40-45 depend from and contain all the limitations of claim 1, these claims are felt to distinguish patentably from the cited prior art in the same way as claim 1. Similarly, claim 46 which uses an agent which inhibits both P-selectin and L-selectin, and claim 47 which uses a first agent which inhibits P-selectin and a second agent which inhibits E-selectin, are also felt to distinguish patentably from the cited prior art. And, claim 38 which is directed to a therapeutic agent for treating atherosclerosis which inhibits both P- and E-selectin is also patentable for the reasons discussed above.

Claims 1-12, 19, 20, 26-38 and 40-47 have been rejected under 35 U.S.C. §103 as being unpatentable over Rohrer, in view of DeAmbrosi, further in view of Ross, and further in view of Johnson-Tidey. The Examiner states:

It would have been obvious for a person of ordinary skill in the art at the time of the invention to use heparin or its derivatives in a method of treatment or prevention of atherosclerosis wherein the method requires inhibition of the interaction between P-selectin and its ligand.... Furthermore, Johnson-Tidey confirms that both P- and E-selectin are known to be involved with atherosclerosis.

Applicants respectfully traverse this rejection.

Rohrer teaches that heparin in high concentrations is a potent inhibitor of platelet degranulation. The studies were carried out using flow cytometry to quantitate the extent of



platelet degranulation by measurement of the platelet surface binding of a GMP-140 specific mAb (see Abstract). Rohrer does not teach a method for treating atherosclerosis comprising administering an agent that inhibits both P and E selectins.

DeAmbrosi teaches certain epoxy-heparide polysaccharides and discusses their use in treating atherosclerosis. DeAmbrosi does not teach a method for treating atherosclerosis comprising administering an agent that inhibits both P and E selectins.

Ross and Johnson-Tidey are discussed above.

In sum, none of the cited prior art, either singly or in combination, teaches or suggests a method for treating or inhibiting atherosclerosis by providing an agent which inhibits interaction between P-selectin and its ligand and between E-selectin and its ligand. Even if one made the combination suggested by the Examiner, it would not meet the limitations recited in the claims under rejection. Most significantly, there is no teaching or suggestion whatsoever in the cited prior art of the advantages that are present in applicants' claimed invention, i.e., that an inhibitor of P-selectin and E-selectin has additive effects in treating atherosclerosis (as shown in Exhibit K, Figs. 1-5, discussed above). Such additive effects resulting from applicants' claimed invention are unexpected and surprising.

Since claims 2-12, 19, 20, 26-37 and 40-45 depend from and contain all the limitations of claim 1, these claims are felt to

distinguish patentably from the cited prior art in the same way as claim 1. For similar reasons, claims 38, 46 and 47 are also believed to be patentably distinct from the cited prior art.

Summary

In view of the above, it is respectfully submitted that the claims are in condition for allowance and such action is requested.

If the Examiner will not allow this application upon receipt and consideration of this amendment, it is respectfully requested that the Examiner call applicants' undersigned counsel prior to final action in order to discuss the issues and advance the prosecution of the application.

Respectfully submitted,

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